

RUBRAMIN PC - cyanocobalamin injection, solution

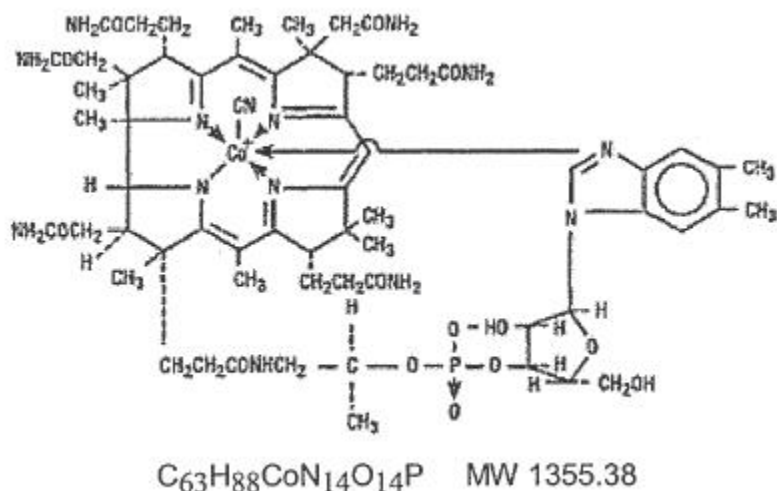
Bristol-Myers Squibb Company

DESCRIPTION

Rubramin PC (Cyanocobalamin Injection) contains cyanocobalamin (vitamin B₁₂) in a clear, red, sterile, nonpyrogenic, aqueous solution in a potency of 1000 mcg/mL (cobalt: 40 mcg/mL) for intramuscular use. Each mL of solution also contains 10 mg benzyl alcohol as a preservative and sodium chloride for isotonicity; pH has been adjusted between 4.5 and 7.0 with sodium hydroxide or hydrochloric acid.

Cyanocobalamin is very hygroscopic in the anhydrous form, and sparingly soluble in water (1:80). The vitamin B₁₂ coenzymes are very unstable in light.

Cyanocobalamin may be chemically designated as 5,6-dimethyl-benzimidazolyl cyanocobamide. The structural formula is represented below:



CLINICAL PHARMACOLOGY

Vitamin B₁₂ is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis.

Cyanocobalamin is quantitatively and rapidly absorbed from intramuscular sites of injection; the plasma level of the compound reaches its peak within one hour after intramuscular injection. Absorbed vitamin B₁₂ is transported via specific B₁₂ binding proteins, transcobalamin I and II to the various tissues. The liver is the main organ for vitamin B₁₂ storage.

Within 48 hours after injection of 1000 mcg of vitamin B₁₂, 50 to 98 percent of the injected dose may appear in the urine. The major portion is excreted within the first eight hours.

Gastrointestinal absorption of vitamin B₁₂ depends on the presence of sufficient intrinsic factor and calcium ions. Intrinsic factor deficiency causes pernicious anemia, which may be associated with subacute combined degeneration of the spinal cord. Prompt parenteral administration of vitamin B₁₂ prevents progression of neurologic damage.

The average diet supplies about 5 to 15 mcg/day of vitamin B₁₂ in a protein-bound form that is available for absorption after normal digestion. Vitamin B₁₂ is not present in foods of plant origin, but is abundant in foods of animal origin. In people with normal absorption, deficiencies have been reported only in strict vegetarians who consume no products of animal origin (including milk products or eggs).

Vitamin B₁₂ is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and vitamin B₁₂ enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1 percent of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. Oral absorption is considered too unreliable in patients with pernicious anemia or other conditions resulting in malabsorption of vitamin B₁₂.

Cyanocobalamin is the most widely used form of vitamin B₁₂, and has hematopoietic activity apparently identical to that of the anti-anemia factor in purified liver extract. Hydroxycobalamin is equally as effective as cyanocobalamin, and they share the cobalamin molecular structure.

INDICATIONS AND USAGE

Rubramin PC is indicated for use as the flushing dose in the Schilling (vitamin B₁₂ absorption) Test for pernicious anemia.

CONTRAINDICATIONS

This preparation is contraindicated in patients who are sensitive to cobalt and/or vitamin B₁₂.

WARNINGS

Patients who have early Leber's disease (hereditary optic nerve atrophy) have been found to suffer severe and swift optic atrophy when treated with vitamin B₁₂.

Fatal hypokalemia may occur when severe megaloblastic anemia is treated intensively with vitamin B₁₂, as a result of increased erythrocyte potassium requirements (see PRECAUTIONS, Laboratory Tests).

Anaphylactic shock and death have been reported after parenteral vitamin B₁₂ administration. An intradermal test dose is recommended before cyanocobalamin is administered to patients suspected of being sensitive to this drug.

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

PRECAUTIONS

General

Doses of vitamin B₁₂ exceeding 10 mcg daily may produce a hematologic response in patients who have a folate deficiency.

Indiscriminate administration of vitamin B₁₂ may mask the true diagnosis of pernicious anemia.

Vitamin B₁₂ deficiency that is allowed to progress for longer than three months may produce permanent degenerative lesions of the spinal cord. Doses of folic acid greater than 0.1 mg per day may result in hematologic remission in patients with vitamin B₁₂ deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B₁₂, irreversible damage will result.

Laboratory Tests

Patients with pernicious anemia have about three times the incidence of carcinoma of the stomach as the general population, so appropriate tests for this condition should be carried out when indicated.

Drug Interactions

Neomycin, colchicine, para-aminosalicylic acid, or excessive alcohol intake longer than two weeks may cause malabsorption of vitamin B₁₂. Chloramphenicol and other drugs having bone marrow suppressant properties may cause a lack of therapeutic response to vitamin B₁₂; this effect may be due to interference with erythrocyte maturation.

Drug/Laboratory Test Interactions

Most antibiotics, methotrexate, and pyrimethamine invalidate folic acid and vitamin B₁₂ diagnostic microbiological blood assays.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential have not been done. There is no evidence from long-term use in patients with pernicious anemia that cyanocobalamin is carcinogenic. Pernicious anemia is associated with an increased incidence of carcinoma of the stomach, but this is believed to be related to the underlying pathology and not to treatment with cyanocobalamin.

Pregnancy

Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B₁₂ is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B₁₂ that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for pregnant women (4 mcg daily) should be consumed during pregnancy.

Nursing Mothers

Vitamin B₁₂ is known to be excreted in human milk. Amounts of vitamin B₁₂ that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for lactating women (4 mcg daily) should be consumed during lactation. Vitamin B₁₂ appears in the milk of nursing mothers in concentrations that approximate the mother's vitamin B₁₂ blood level.

Pediatric Use

Safety and effectiveness in pediatric patients has not been established.

ADVERSE REACTIONS

No serious toxic reactions have been reported following the intramuscular administration of cyanocobalamin. The following allergic-type reactions have been reported rarely; the relationship of these reactions to cyanocobalamin or other components in the preparation is unknown.

Generalized—anaphylactic shock and death have been reported with administration of parenteral vitamin B₁₂ (see WARNINGS)

Cardiovascular—pulmonary edema and congestive heart failure early in treatment, peripheral vascular thrombosis

Hematologic—polycythemia vera

Gastrointestinal—mild transient diarrhea

Dermatologic—itching, transitory exanthema, urticaria
Miscellaneous—feeling of swelling of entire body

OVERDOSAGE

No overdosage has been reported with this drug.

DOSAGE AND ADMINISTRATION

Rubramin PC (Cyanocobalamin Injection) should be visually inspected for particulate matter and color prior to administration; the solution is clear red.

Do not administer intravenously.

Schilling Test*

The flushing dose is 1000 mcg injected intramuscularly. For procedure see the insert packaged with Rubratope[®]-57 (Cyanocobalamin Co 57) capsules or diagnostic kit (see the DOSAGE AND ADMINISTRATION section).

HOW SUPPLIED

Rubramin PC (Cyanocobalamin Injection USP)

Unimatic[®] Single Dose Syringes

The syringes are supplied with sterile disposable 22-gauge, 1-1/4-inch needles.

1000 mcg (1 mL): NDC 0270-0519-16

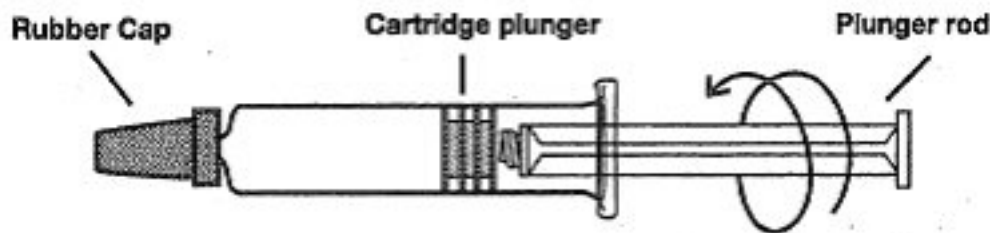
Storage

Protect from light (keep syringes in carton). Store at controlled room temperature; avoid freezing.

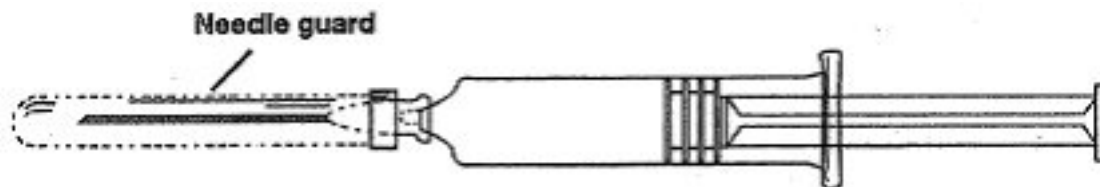
Directions for Use of

UNIMATIC[®] *single dose syringe*

- 1) Screw the threaded tip of the plunger rod clockwise into the cartridge plunger and push forward a few millimeters to break any friction between the cartridge plunger and syringe barrel.



- 2) Holding syringe erect, aseptically remove the rubber cap from the tip of the syringe and attach the sterile, disposable needle using a push-twist action.



- 3) Remove the needle guard, hold the syringe erect, and push plunger forward until a drop appears at tip of needle and all of the air is evacuated. Following the usual aspiration procedure complete the injection.
- 4) Destroy the needle and syringe immediately after use.

Manufactured for

Bracco Diagnostics Inc.

Princeton, N.J. 08543

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